

JP 2002-293773 English Translation

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Notes:

1. Untranslatable words are replaced with asterisks (* **).
2. Texts in the figures are not translated and shown as it is.

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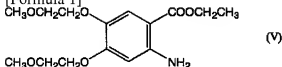
Dictionary: Last updated 04/11/2008 / Priority:

CLAIM + DETAILED DESCRIPTION

[Claim(s)]

[Claim 1] Formula (V)

[Formula 1]



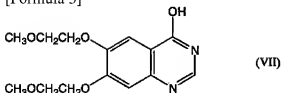
the 2-amino 4 and the 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base which are come out of and shown, and formula (VI)

[Formula 2]



The formula (VII) characterized by coming out and carrying out the closed ring reaction of the ammonium formate shown

[Formula 3]

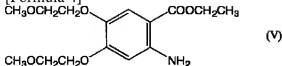


4-hydroxy 6, the manufacture method of 7-bis(2-methoxyethoxy) quinazoline which are come out of and shown.

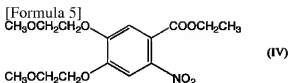
[Claim 2] The method according to claim 1 characterized by performing a closed ring reaction at 120-140 degrees C.

[Claim 3] Formula (V)

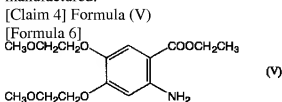
[Formula 4]



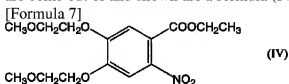
the 2-amino 4 and the 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base which are come out of and shown -- formula (IV)



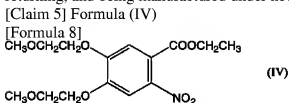
The method according to claim 1 or 2 characterized by coming out, returning the 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl shown, and being manufactured.



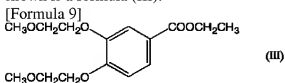
The 2-amino 4 and the 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base which are come out of and shown are a formula (IV) in methanol.



The method according to claim 1 or 2 which comes out, makes the 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl shown platinum / carbon catalyst, and is characterized by for sponge nickel catalyst existence sewer matter-ization returning, and being manufactured under neutral conditions.



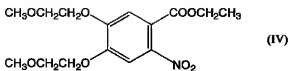
The 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl come out of and shown is a formula (III).



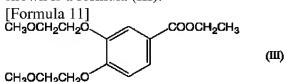
The method according to claim 3 or 4 characterized by coming out, nitrating the 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl shown, and being manufactured.

[Claim 6] Formula (IV)

[Formula 10]

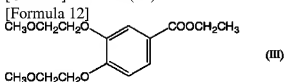


The 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl come out of and shown is a formula (III).

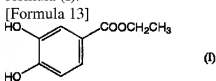


The method according to claim 3 or 4 characterized by coming out, nitrating the 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl shown using the mixed acid of sulfuric acid-nitric acid, and being manufactured.

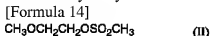
[Claim 7] Formula (III)



The 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl come out of and shown is a formula (I).



3 and 4-dihydroxy benzoic acid ethyl come out of and shown, and a formula (II)



The method according to claim 5 or 6 characterized by coming out, making the MESHIRU acid 2-METOKISHI ethyl ester shown react, and being manufactured.

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the manufacture method of 6 [useful as an anticancer drug], 4-hydroxy 6 which are the important middle object of 7-bis(2-methoxyethoxy)-4-(3-ECHINIRU phenyl) amino quinazoline (USP No. 5747498), and 7-bis(2-methoxyethoxy) quinazoline.

[0002]

[Description of the Prior Art] 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline is the important middle object of useful as anticancer drug 6, and 7-bis(2-methoxyethoxy)-4-(3-

ECHINIRU phenyl) amino quinazoline (USP No. 5747498). 4-hydroxy 6 [given in a USP No. 5747498 Description], and the manufacture method of 7-bis(2-methoxyethoxy) quinazoline, The first reaction which flow back for 64 hours, and 2-METOKISHI ethyl star's picture, 3, and 4-dihydroxy benzoic acid ethyl and potassium carbonate are made to react using an iodination tetrabutylammonium catalyst, and obtains 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl among an acetone solvent, The second reaction which the 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl obtained by the first reaction is made to react with the inside of an acetic acid solvent, and 4Eq nitric acid for 24 hours, and obtains 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, The 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl obtained by the second reaction under hydrogen chloride existence and in ethanol The third reaction which carries out hydrogenation reduction under pressurization and obtains the 2-amino 4 and 5-bis(2-methoxyethoxy) benzoic acid ethyl chloride salt using a platinum oxide catalyst, The 2-amino 4 and 5-bis(2-methoxyethoxy) benzoic acid ethyl chloride salt which were obtained by the third reaction, and ammonium formate are made to react at 160-165 degrees C among HORUMU amide for 3 hours. It consists of the fourth reaction which obtains 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline. Since hydrogenation reduction using the platinum oxide catalyst of the third reaction is performed under hydrogen chloride existence, the output of the third reaction is taken out as chloride salt. [0003] However, the fourth reaction has the following problems from the first reaction of the above-mentioned method, respectively. That is, since the first reaction is a compound with which 2-METOKISHI ethyl star's picture which is materials is expensive, and economical efficiency is missing, and mutagenicity is suspected, it lacks in safety. Furthermore, since reaction time requires the long time of 64 hours, it is hard to call it an advantageous process industrially. Reaction time requires 24 hours and the second reaction does not have it. [efficient] Since the third reaction has the fault which uses as much as about 20 times the amount of ethanol to materials and uses expensive platinum oxide, it lacks in economical efficiency, and since hydrogenation reduction is further carried out under pressurization, it requires special equipment. Moreover, when the method of depending on this third reaction is retested, there is a problem that the impurities which are hard to remove to the 2-amino 6 and 7-bis(2-methoxyethoxy) benzoic acid ethyl which are obtained generate. This is presumed to be a side reaction by chloride. Since the fourth reaction has the reactivity of the chloride salt which is the output of the third reaction lower than the isolation base There is a fault from which output is not obtained unless it is not suitable for industrial manufacture and carries out complicated extraction and refining operation after a reaction using chloroform which is a halogenation thing solvent, since reaction temperature as high as 160-165 degrees C is needed.

[0004]

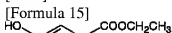
[Problem(s) to be Solved by the Invention] The manufacture method of 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline is offered from 3 [economical / this invention /, safe, and efficient] and 4-dihydroxy benzoic acid ethyl. Moreover, this invention is efficient. And the manufacture method of 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline is offered from 4 which is a middle object, 3 with sufficient **** of 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, and 4-bis(2-methoxyethoxy) benzoic acid ethyl. Furthermore, equipment economical [this invention] and special is

not required, but there is also no problem that the impurities which are hard to remove to output arise. And the manufacture method of 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline is offered from 4 with sufficient **** of 2-amino [which is a middle object] 4, and 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base, and 5-bis(2-methoxyethoxy)-2-nitrolycerine benzoic acid ethyl. Moreover, can react at low temperature more and complicated extraction and refining operation are not needed. [base / 4-hydroxy 6 of high purity, the 2-amino 4 which can obtain 7-bis(2-methoxyethoxy) quinazoline, and / 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation / and the manufacture method of 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline] It provides.

[0005]

[Means for Solving the Problem] This invention persons are formulas (I) as a result of inquiring about each process of the fourth reaction from the first reaction about the manufacture method of 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline.

[0006]

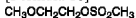


(I)

[0007] 3 and 4-dihydroxy benzoic acid ethyl (it is called the following "Compound I".) come out of and shown, and a formula (II)

[0008]

[Formula 16]



(II)

[0009] It is [safe from inexpensive materials] a formula (III) efficiently by coming out and making the MESHIRU acid 2-METOKISHI ethyl ester (it being called the following "Compound II".) shown react.

[0010]



(III)

[0011] It found out that it came out and the 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl (it is called the following "Compound III".) shown could be manufactured.

Moreover, this invention persons are formulas (IV) with efficiently and sufficient **** by nitrating Compound III using the mixed acid of sulfuric acid-nitric acid.

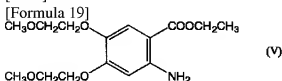
[0012]



(IV)

[0013] It found out that it came out and the 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl (it is called the following "Compound IV".) shown could be manufactured. Furthermore, this invention persons also set Compound IV under a neutral condition without acid among methanol. It is a formula (V) with **** using an inexpensive reagent, do not require special equipment, but there is also no problem that the impurities which are hard to remove to output arise, and sufficient platinum / carbon catalyst, or by sponge-nickel-catalyst-existence-sewer-matter--ization-returning.

[0014]



[0015] It found out that it came out and the 2-amino 4 and the 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base (it is called the following "Compound V".) which are shown could be manufactured. Moreover, this invention persons are Compound V and the formula (VI) which are an isolation base.

[0016]

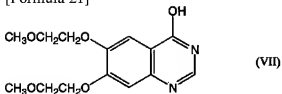
[Formula 20]



[0017] By coming out and carrying out the closed ring reaction of the ammonium formate (it being called the following "Compound VI".) shown, it can react at low temperature more, complicated extraction and refining operation are not needed, and it is a formula (VII) to high purity.

[0018]

[Formula 21]



[0019] It found out that it came out and the 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline (it is called the following "Compound VII".) shown could be manufactured. Namely, it is characterized by this invention carrying out the closed ring reaction of the compound V which is (1) isolation base, and the compound VI. The manufacture method of Compound VII, and (2) closed ring reaction The method given in 120 - (1) characterized by carrying out at 140 degrees C, (3) The compound V which are the method of (1) or (2) descriptions by which it is characterized, and (4) isolation base the compound V which is an isolation base returning Compound IV, and being manufactured in methanol Compound IV under neutral conditions Platinum / carbon catalyst, or a method (1) characterized by being returned and manufactured, or given in sponge nickel catalyst existence sewer matter-ized (2), (5) (3) or the method given in (4) characterized by for Compound IV nitrating Compound III and manufacturing it, (6) It is related with the method (5) or given in (6) characterized by for a method (3) characterized by for

Compound IV nitrating Compound III using the mixed acid of sulfuric acid-nitric acid, and manufacturing it or given in (4) and the (7) compound III making Compound I and Compound II react, and manufacturing them.

[0020]

[Embodiment of the Invention] This invention is explained in detail hereafter.

[0021] The 3 and 4-dihydroxy benzoic acid ethyl itself used as materials is a known compound, and it can also use as it is what can use what was manufactured by the well-known method, or is marketed.

[0022] The manufacture method MESHIRU acid 2-METOKISHI ethyl ester of MESHIRU acid 2-METOKISHI ethyl ester can manufacture 2-METOKISHI ethanol and MESHIRU chloride by carrying out an esterification reaction under existence of a base preferably. An esterification reaction can be performed by, for example, dropping MESHIRU chloride at the solution which dissolved 2-METOKISHI ethanol and a base in the solvent. Moreover, it can also carry out by dropping a base after flowing MESHIRU chloride into **** of 2-METOKISHI ethanol and a solvent. As for the amount of the MESHIRU chloride used, 1.0-1.3mol per 1mol of 2-METOKISHI ethanol is desirable. As a solvent, a tetrahydro franc, toluene, a halogenation thing solvent, etc. are mentioned. As for the amount of the solvent used, 3-10ml is desirable to 2-METOKISHI ethanol 1g. As a base, triethyl amine, N-methyl morpholine, PIRIJIN, JIMECHIRU aniline, etc. are mentioned. As for the amount of the base used, 1.0-1.5mol per 1mol of 2-METOKISHI ethanol is desirable. Reaction time's 2.5 to 5 hours are desirable, and -10-20 degree C of reaction temperature is desirable. Although MESHIRU acid 2-METOKISHI ethyl ester can filter and carry out after-concentration distillation under reduced pressure of the reaction liquid and can use it for the next reaction, when good in purity, you may use it for the next reaction with the state where reaction liquid was filtered and condensed.

[0023] [ethyl / 3 and 4-dihydroxy benzoic acid / 3, the manufacture method 3 of 4-bis(2-methoxyethoxy) benzoic acid ethyl, and 4-bis(2-methoxyethoxy) benzoic acid ethyl] 3 and 4-dihydroxy benzoic acid ethyl and MESHIRU acid 2-METOKISHI ethyl ester can be preferably manufactured by making it react under catalyst existence under existence of a base. The reaction can dissolve 3 and 4-dihydroxy benzoic acid and a catalyst in a solvent, and can be performed by dropping MESHIRU acid 2-METOKISHI ethyl ester after adding a base, for example.

[0024] 2-3mol per 1mol of 3 and 4-dihydroxy benzoic acid ethyl of the amount of the MESHIRU acid 2-METOKISHI ethyl ester used is 2.1-2.6mol preferably. When using the MESHIRU acid 2-METOKISHI ethyl ester obtained at the pre- reaction, without isolating, it is desirable to use the quantity substantially contained in this range.

[0025] As a solvent, acetone, methyl ethyl ketone, a tetrahydro franc, Solvents, such as JIMECHIRUHORUMU amide (DMF), dimethyl sulfoxide (DMSO), 1, 3-*****- 2-imidazolidinone, and t-butanol, are mentioned, and acetone and DMF are more desirable than viewpoints, such as economical efficiency and handling nature. As amount of the solvent used, 6-18ml is 8-16ml preferably to 3 and 4-dihydroxy benzoic acid ethyl 1g.

[0026] As a base, potassium carbonate, sodium carbonate, t-butoxy potassium, t-butoxy sodium, sodium hydride, etc. are mentioned, and potassium carbonate and t-butoxy potassium are more desirable than the viewpoint of reactivity and safety. As amount of the base used, 2.0-5.0mol per 1mol of 3 and 4-dihydroxy benzoic acid ethyl is 2.1-3.0mol preferably from the viewpoint of reactivity and economical efficiency.

[0027] As a catalyst, iodides, such as potassium iodide and sodium iodide, are mentioned and sodium iodide is more desirable than a reactant viewpoint. Moreover, you may use a ** move catalyst as a catalyst. As a ** move catalyst, iodination tetrabutylammonium (TBAI), iodination benzoRUTORI methylammonium, bromination tetrabutylammonium, etc. are mentioned, and iodination tetrabutylammonium is more desirable than the viewpoint of reactivity and economical efficiency. as the amount of the catalyst used -- 3 and 0.5 per 4-dihydroxy benzoic acid ethyl 100 weight part - 10 weight part -- it is 1 - 5 weight part preferably.

[0028] As reaction temperature, 30-100 degrees C is 50-80 degrees C preferably. Although based also on the amount of the materials used as reaction time, it is 5 to 20 hours. Liquid chromatography (HPLC) analyzes the end of a reaction and 3 and 4-dihydroxy benzoic acid ethyl and its Monod 2-methoxyethoxy-ized middle object should just be 0.5% or less.

[0029] As the processing method after a reaction, **** is condensed after filtering an insoluble matter, for example, and the way general-purpose solvents, such as toluene, extract water after flowing is mentioned to the method of crystallizing by n-Cheb Than, or a concentration residual substance.

[0030] [ethyl / 3 and 4-bis(2-methoxyethoxy) benzoic acid / 4, the manufacture method 4 of 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl] It can manufacture by nitrating 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl. Although nitration can be performed by the usual method using the mixture (mixed acid) of nitric acid and sulfuric acid, nitrogen oxide, etc., it is desirable to use mixed acid. For example, by the method of using mixed acid, 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl can be dissolved in a solvent, sulfuric acid can be added, and it can carry out by subsequently dropping nitric acid. 15-40 degrees C of dropping temperature of nitric acid is 20-35 degrees C preferably.

[0031] As a solvent, acetic acid, nitroglycerine benzene, and nitroglycerine methane are mentioned, and acetic acid is desirable from a viewpoint of safety. As amount of the solvent used, 200-500ml per 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl 100g is 250-350ml preferably.

[0032] When using mixed acid, sulfuric acid can use 86 to 98% of sulfuric acid, and 93 to 98% of its sulfuric acid is desirable. as the amount of the sulfuric acid used -- 5 per 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl 100 weight part - 30 weight part -- it is 10 - 20 weight part preferably. If there are few amounts of sulfuric acid, a reaction will become slow, and if there are many amounts of sulfuric acid, side reactions, such as dinitro-izing, will occur easily. 65 to 75% of nitric acid of nitric acid is desirable, and its nitric acid which is about 75% is still more desirable. 2.5-3.5mol per 1mol of 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl of the amount of the nitric acid used is 2.8-3.2mol preferably. The amount of sulfuric acid and the nitric acid used has 3-6.5mol of desirable nitric acid to 1mol of sulfuric acid.

[0033] 20-40 degrees C of reaction temperature is usually 25-35 degrees C preferably. Although reaction time is based also on the amount of the materials used, it is usually 3 to 6 hours.

[0034] The end of a reaction is analyzed by HPLC and materials should just be 0.2% or less.

[0035] As a method of processing after a reaction, it is based on the following method,

for example. First, reaction liquid is dropped underwater. the quantity of water receives a 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl 100 weight part -- a 350 - 600 weight part -- it is a 450 - 550 weight part preferably. Solvents, such as toluene, ethyl acetate, and a halogenation thing solvent, extract 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl from the obtained solution. As an amount of solvents, it is 500-1500ml per 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl 100g. In order to raise extraction efficiency, you may extract in several steps. Bicarbonate-of-soda water and water wash the extracting solvent containing 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, respectively in order to remove acid content. The solution containing 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl is condensed under decompression, and distills off a solvent. A concentration residual substance is only about 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, and can be used for the following process as it is.

[0036] [ethyl / 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid / the 2-amino 4, the manufacture method 2-amino 4 of a 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base, and a 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base] It can manufacture by returning 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl. Although reduction can be performed by the usual methods, such as the method of carrying out hydrogenation reduction using a catalyst, the method of carrying out hydrogen addition using a reducing agent, and a method that combined these, its method of carrying out hydrogenation reduction using a catalyst is desirable. For example, when using platinum / carbon catalyst, or a sponge nickel catalyst, 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl can be dissolved in a solvent, platinum / carbon catalyst, or a sponge nickel catalyst can be added, and hydrogenation reduction can be carried out under hydrogen atmosphere. Although the hydrogenation reduction reaction using platinum / carbon catalyst, or a sponge nickel catalyst can be performed under normal pressure, you may carry out under pressurization.

[0037] Although methanol, ethanol, isopropyl alcohol, toluene, etc. are mentioned as a solvent, the viewpoint of reactivity, safety, and economical efficiency to methanol is desirable. The amount of the solvent used is 700-900ml to 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl 100g.

[0038] Although platinum/carbon (Pt/C), sponge nickel (Raney nickel), palladium/carbon (Pd/C), etc. are used as a catalyst of hydrogenation reduction, platinum / carbon, or sponge nickel is desirable. As platinum/carbon, what contains platinum 3 to 10% is desirable. When using 5% platinum / carbon support article, it is desirable to use 3 - 8 weight part as a platinum metal to a 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl 100 weight part. What is usually used for reduction can be used for sponge nickel, it makes sodium hydroxide heat solution what contains nickel 40 to 50% as an alloy with aluminum preferably act, and melts aluminum away, and what was used as the water distribution article can be used for it. Moreover, what is marketed can be used for sponge nickel (for example, deployment nickel R-200: made by Nikko Rica Corp.).

[0039] When using sponge nickel as a catalyst, it is desirable to use 5 - 20 weight part to a 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl 100 weight part as a sponge nickel water distribution article (40 to 50% of nickel content). Moreover, although methanol, ethanol, etc. are mentioned as a solvent, the viewpoint of reactivity,

safety, and economical efficiency to methanol is desirable. These solvents may contain about 10% of water. As for the amount of the solvent used in the case of using sponge nickel, 300-1000ml is desirable to 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl 100g.

[0040] It is desirable to perform a reaction under neutral conditions. here -- neutral conditions -- pH 5-8 -- it is pH 7-8 preferably.

[0041] 10-40 degrees C of reaction temperature is 20-40 degrees C preferably. When using sponge nickel as a catalyst, 35-55 degrees C of reaction temperature are desirable. Reaction time is usually 5 to 10 hours preferably for 5 to 20 hours. The end of a reaction is a time of absorption of hydrogen finishing mostly, and a time of analyzing by HPLC and materials becoming 0.5% or less.

[0042] The processing after a reaction carries out filtration separation of the catalyst, for example, condenses filtrate under decompression, or extracts it with organic solvents, such as after-concentration toluene and a methylene chloride, and 5%, subsequently it can wash with water and it can be performed rare alkali, such as bicarbonate-of-soda water, and by carrying out vacuum concentration of the solvent.

[0043] [base / the 2-amino 4 and / 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation / 4-hydroxy 6, manufacture method 4-hydroxy 6 of 7-bis(2-methoxyethoxy) quinazoline, and 7-bis(2-methoxyethoxy) quinazoline] It can manufacture by the closed ring reaction of the 2-amino 4, a 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base, and ammonium formate. A reaction can be performed by adding the 2-amino 4, a 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base, and ammonium formate to a solvent, and carrying out churning heating, for example.

[0044] 1-4mol of the amount of the ammonium formate used is 1-2.5mol preferably to the 2-amino 4 and 1mol of 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation bases.

[0045] As a solvent, HORUMU amide, DMF, DMSO, etc. are mentioned and HORUMU amide is desirable from a reactant viewpoint. As amount of the solvent used, 150-250ml per the 2-amino 4 and 100g of 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation bases is desirable.

[0046] 120-140 degrees C of reaction temperature is 125-140 degrees C preferably. Although reaction time is based also on the amount of the materials used, it is usually 8 to 15 hours. The end of a reaction is a time of analyzing by HPLC and materials becoming 0.5% or less.

[0047] The post-processing of a reaction can wash the solid which filtered [flowed, cooled further, was made to crystallize it and] and separated acetonitrile or iso propanol by acetonitrile or iso propanol after cooling a reaction mixture at about 80 degrees C, for example, and can perform it by drying. Acetonitrile or iso propanol may contain water about 5%.

[0048]

[Example] Although a work example is given and this invention is explained concretely hereafter, this invention is not limited to these work examples.

[0049] Work example 1 Manufacture 2-METOKISHI ethanol of MESHIRU acid 2-METOKISHI ethyl ester (114.2 g, 1.5 mol), MESHIRU chloride (171.8 g, 1.5 mol) was dropped at the tetrahydro franc (343 ml) solution of N-methyl morpholine (166.9 g, 1.65 mol) at 0-20 degrees C. At 10-20 degrees C, after about 2.5-hour maturing, filtration concentration was carried out and MESHIRU acid 2-METOKISHI ethyl ester (238.4 g)

was obtained. Gas chromatograph area percentage purity was 89.8%. Furthermore, distillation under reduced pressure of the MESHIRU acid 2-METOKISHI ethyl ester (48.5 g) was carried out by 101-104 degrees C / 0.4KPa, and MESHIRU acid 2-METOKISHI ethyl ester (44.3 g) was obtained as a colorless liquid. It was 94.2% of isolation ****.

¹H-NMR delta(ppm in CDCl₃, 400 MHz): 3.06(3H, s); 3.41(3H, s); 3.66, 4.37 (2H each, m) [0050] Work example 2 Manufacture 2-METOKISHI ethanol of MESHIRU acid 2-METOKISHI ethyl ester (114.2 g, 1.5 mol) Triethyl amine (152.0 g, 1.5 mol) was dropped at 0-2 degrees C after flowing MESHIRU chloride (171.8 g, 1.5 mol) into the included toluene solution (426 g). At 10-20 degrees C, after about 2.5-hour maturing, it flowed and churning liquid separation of the water (200 ml) was carried out. Oil (198.0 g) was obtained after condensing a toluene layer, distillation under reduced pressure of it was carried out, and MESHIRU acid 2-METOKISHI ethyl ester (166.2 g) was obtained. It was 71.8% of isolation ****.

[0051] Work example 3 MESHIRU acid 2-METOKISHI ethyl ester is used without isolating, the method 3 of manufacturing 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl from 3 and 4-dihydroxy benzoic acid ethyl, and 4-dihydroxy benzoic acid ethyl (3.64 g, 0.02 mol) In the DMF (35 ml) solution of TBAI (0.25 g), t-butoxy potassium (5.61 g, 0.05 mol) at 20-40 degrees C After addition, The rough MESHIRU acid 2-METOKISHI ethyl ester (13.6 g - 0.08 mol) compounded in the work example 1 before carrying out distillation refining was dropped. After agitating reaction liquid at 30-40 degrees C for 10 hours, it neutralized with chloride 35%. Water washed toluene (100 ml) after flowing, and it dried with anhydrous sodium sulfate. Oil was obtained after filtration concentration and it was made to crystallize by Cheb Than (30 ml). The crystal was separated and 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl (5.40 g) was obtained after washing and dryness by Cheb Than. **** was 90.5%.

¹H-NMR(inch CDCl₃, 400 MHz) delta ppm 7.66 (1H, dd, J= 2.0, 8.3) Hz; 7.59 (1H, d, J=2.0) Hz; 6.91(1H, d, J=8.3 Hz); 4.34(2H, q, J=7.0 Hz); 4.20, 3.80(4H each, m); 3.47, 3.46(3H each, s); 1.38(3H, t, J=7.0 Hz) [0052] Work example 4 The distillation article of MESHIRU acid 2-METOKISHI ethyl ester is used, the method 3 of manufacturing 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl from 3 and 4-dihydroxy benzoic acid ethyl, and 4-dihydroxy benzoic acid ethyl (87.4 g, 0.48 mol) The MESHIRU acid 2-METOKISHI ethyl ester (190.8 g, 1.24 mol) compounded in the work examples 1 and 2 was dropped at potassium carbonate (146.0 g, 1.06 mol) and the acetone (960 ml) solution of TBAI (2.4 g). Heating flowing back of the reaction liquid was carried out at 60 degrees C for 16 hours. The reaction mixture was filtered and condensed after cooling. Toluene (300 ml) and water (200 ml) were flowed into the obtained concentration residual substance, and churning liquid separation was carried out. It was made to crystallize by Cheb Than (500 ml) after condensing a toluene layer. The crystal was separated and it was made to crystallize by Cheb Than (30 ml) again after dryness. The crystal was separated and 3 and 4-bis(2-methoxyethoxy) benzoic acid ethyl (134.1 g) was obtained after washing and dryness by Cheb Than. **** was 93.8%.

[0053] Work example 5 [ethyl / 3 and 4-bis(2-methoxyethoxy) benzoic acid / 4, the manufacture method 3 of 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, and the acetic acid (157 ml) solution of 4-bis(2-methoxyethoxy) benzoic acid ethyl (52.5 g)] 98% sulfuric acid (8.2 g) Nitric acid (48.3 g) was dropped at 15-35 degrees C 69%

after dropping. Churning was continued till the end of a reaction (about 3 to 4 hours) at 30-35 degrees C. It flowed into water (263 ml) and the reaction mixture was extracted with toluene (230 g). Vacuum concentration of the toluene extraction liquid was carried out after washing one by one with bicarbonate-of-soda water and water 5%, and 4 of shape of orange oil and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl (59.2 g) was obtained. The appearance **** was 98.0% in HPLC area percentage 98.5%. ¹H-NMR(inch CDCl₃,400 MHz) delta in ppm 7.50(1H, s);7.12(1H, s);4.37(2H, q, J=6.9 Hz);4.24,3.80(4H each, m);3.45(6H, s);1.35(3H, t, J=7.0 Hz) [0054] Work example 6 3, 4 from 4-bis(2-methoxyethoxy) benzoic acid ethyl, the manufacture method 3 of 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl, and 4-bis(2-methoxyethoxy) benzoic acid ethyl (105 g) It dissolved in acetic acid (330 g), and sulfuric acid (17.22 g) was added 98%. Nitric acid (96.6 g) was dropped 69% at 15-35 degrees C, and it agitated at 25-35 degrees C for 3 hours. Materials were 0.1% when reaction liquid was analyzed by HPLC. Reaction liquid was dropped at water (525 g), acetic acid (38 g) washed the reaction container, and it added to above *****, toluene (455 g) -- ***** -- in addition, liquids were extracted and separated at 20-30 degrees C. Liquids were further extracted and separated with toluene (455 g), and the water layer was united with the previous organic layer. The organic layer was condensed under decompression, after washing with water (525 g) subsequently, 5% bicarbonate-of-soda water (525 g) and. The concentration thing was 119.5 g and the appearance **** of 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl was 98.7% in HPLC area percentage 97.6%.

[0055] work example 7 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl (123.4 g) which were obtained from 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl in the 2-amino 4 and the manufacture method work example 6 of the 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base It dissolved in methanol (782 g), Pt/C (55.2% wet product, 13.4g) was added 5%, and hydrogenation reduction was carried out under normal pressure and hydrogen atmosphere at the temperature of 20-40 degrees C. After absorption of hydrogen was completed, reaction liquid was filtered, and methanol (195 g) washed the catalyst. It condenses under decompression and they are the 2-amino 4 and a 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base. (106.9 g) It obtained. **** was 95%. HPLC area percentage was 98.1%.

¹H-NMR(inch CDCl₃,400 MHz) delta in ppm 7.45(1H, s);6.15 (1H) s);5.58(br, s);4.27(2H, q, J=6.8 Hz);4.06-4.16, 3.71 to 3.80 (4H each, m); 3.44, 3.40 (3H each, s); 1.36 (3H, t, J=6.8 Hz) [0056] work example 8 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl (2.0g) which were obtained from 4 and 5-bis(2-methoxyethoxy)-2-nitroglycerine benzoic acid ethyl in the 2-amino 4 and the manufacture method work example 6 of the 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base It dissolved in methanol (20ml), sponge nickel (deployment nickel R-200: made by Nikko Rica Corp.) (about 0.2g) was added, and hydrogenation reduction was carried out under temperature and normal pressure 40-50-degree C. After absorption of hydrogen was completed, methanol (5ml) washed filtration and a catalyst. It condensed under decompression and the 2-amino 3 and a 4-bis(2-methoxyethoxy) benzoic acid ethyl isolation base (1.45g) were obtained. They were 80% of ****, and 94.7% of LC area percentage.

[0057] work example 9 The 2-amino 4, 5-screw (2-methoxyethoxy) the 2-amino 4

obtained from the benzoic acid ethyl isolation base in the work example 7 to the manufacture method HORUMU amide (213.8 g) of 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline, and 5-bis(2-methoxyethoxy) benzoic acid ethyl isolation base (106.9 g) and ammonium formate (21.54g) In addition, it agitated at 130-140 degrees C for 10 hours. 65-80 degrees C -- water (21.5 g) -- subsequently iso propanol (420 g) was dropped. The solid which cooled to 0-5 degrees C, filtered, and was separated was washed by iso propanol (120 g). The obtained solid was dried at 60 degrees C, and 4-hydroxy 6 and 7-bis(2-methoxyethoxy) quinazoline (80.8 g) was obtained. **** was 80.5% and HPLC purity was 99.6%.

¹H-NMR(inch CDCl₃,400 MHz) delta in ppm 12.05(1H, s);8.05 (1H) s);7.60(1H, s);7.15(1H, s);4.29, 3.86(4H each, m);3.48(6H, s) ¹³C-NMR(inch CDCl₃,100 MHz) deltac in ppm 162.4 (s), 154.9 (s), 148.8 (s), 145.4(s),142.3(d),115.7(s),109.3(d),106.7(d),70.7(t),70.5(t),68.7(t),68.5(t),59.3(q),59.2(q) [0058]

[Effect of the Invention] By the method of this invention, it is a middle object of useful as anticancer drug 6, and 7-bis(2-methoxyethoxy)-4-(3-ECHINIRU phenyl) amino quinazoline (USP No. 5747498). The useful compound VII can be manufactured safely and efficiently from Compound I using inexpensive materials. Moreover, Compound VII can be efficiently manufactured with sufficient **** from Compound III by this invention. Furthermore, there is also no problem that the impurities which do not require special equipment and cannot remove Compound VII from Compound IV easily to output due to this invention using an inexpensive reagent arise, and it can manufacture with sufficient ****. Moreover, by this invention, from the compound V which is an isolation base about Compound VII, a reaction can be performed more at low temperature, and complicated extraction and refining operation are not needed, and it can manufacture in high purity.